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The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

**Patentanmeldung Nr. Patent application No. Demande de brevet n°**

03022064.4

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For the President of the European Patent Office

Le Président de l'Office européen des brevets  
p.o.

R C van Dijk



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Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:  
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.  
If no title is shown please refer to the description.  
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## Novel imidazopyridine-derivatives

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## Novel Imidazopyridine-Derivatives

### Field of application of the Invention

The invention relates to novel imidazopyridine derivatives, which are used in the pharmaceutical industry for the production of pharmaceutical compositions.

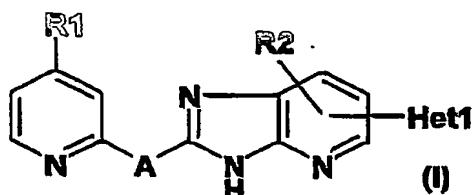
### Known technical background

In the German Patent Application DE 2504252 and in the European Patent Application EP 0125756 3H-imidazo[4,5-b]pyridine derivatives with anti-ulcer activity are described.

### Description of the invention

It has now been found that the novel heteroaryl substituted imidazopyridine derivatives, which are described in greater details below, have surprising and particularly advantageous properties.

The invention thus relates to compounds of formula I



in which

- R1 is 1-4C-alkoxy,
- A is 1-4C-alkylene,
- R2 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,
- Het1 is optionally substituted by R3 and/or R4 and is a monocyclic or fused bicyclic 5- to 10-membered unsaturated or partially saturated heteroaryl radical comprising one to three heteroatoms, each of which is selected from a group consisting of nitrogen, oxygen and sulfur, in which
  - R3 is 1-4C-alkyl, halogen, cyano, trifluoromethyl, phenyl, mono- or di-1-4C-alkylamino, formyl, 1-4C-alkylcarbonyl, carboxyl or 1-4C-alkoxy,
  - R4 is 1-4C-alkyl or halogen.

as well as to the salts, N-oxides and the salts of the N-oxides of these compounds.

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Compounds according to this invention worthy to be mentioned are those compounds of formula I in which

- R1 is methoxy,
- A is ethylene,
- R2 is hydrogen,
- Het1 is optionally substituted by R3 and/or R4 and is a monocyclic or fused bicyclic 5- to 10-membered unsaturated or partially saturated heteroaryl radical comprising one to three heteroatoms, each of which is selected from a group consisting of nitrogen, oxygen and sulfur, in which
- R3 is 1-4C-alkyl, halogen, cyano, trifluoromethyl, phenyl, mono- or di-1-4C-alkylamino, formyl, 1-4C-alkylcarbonyl, carboxyl or 1-4C-alkoxy,
- R4 is 1-4C-alkyl or halogen,

as well as the salts, N-oxides and the salts of the N-oxides of these compounds.

1-4C-Alkyl is a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Examples are the butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl, ethyl and methyl radicals.

1-4C-Alkylene is a straight chain alkylene radical having 1 to 4 carbon atoms. Examples which may be mentioned in this context are the methylene (-CH<sub>2</sub>-), ethylene (-CH<sub>2</sub>-CH<sub>2</sub>-), trimethylene (-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-) and the tetramethylene (-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-) radical.

1-4C-Alkoxy is a radical which, in addition to the oxygen atom, contains a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Alkoxy radicals having 1 to 4 carbon atoms which may be mentioned in this context are, for example, the butoxy, isobutoxy, sec-butoxy, tert-butoxy, propoxy, iso-propoxy, ethoxy and methoxy radicals.

Mono- or Di-1-4C-alkylamino radicals contain in addition to the nitrogen atom, one or two of the abovementioned 1-4C-alkyl radicals. Preferred are the di-1-4C-alkylamino radicals, especially the dimethylamino, the diethylamino and the diisopropylamino radical.

1-4C-Alkylcarbonyl represents a radical which, in addition to the carbonyl group, contains one of the abovementioned 1-4C-alkyl radicals. An example which may be mentioned is the acetyl radical.

Halogen within the meaning of the present invention is bromine, or preferably chlorine or fluorine.

N-oxide denotes the N-oxide on the pyridine which is substituted by R1.

Het1 is optionally substituted by R3 and/or R4 and refers to a monocyclic or fused bicyclic 5- to 10-membered unsaturated or partially saturated heteroaryl radical comprising one to three heteroatoms, each of which is selected from a group consisting of nitrogen, oxygen and sulfur. Particularly, Het1 is

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optionally substituted by R3 and/or R4 and refers to a monocyclic or fused bicyclic 5- to 10-membered unsaturated heteroaryl (heteroaromatic) radical comprising one to three heteroatoms, each of which is selected from a group consisting of nitrogen, oxygen and sulfur.

Exemplary Het1 radicals may be optionally substituted by R3 and/or R4 and may include, without being restricted to, thiophenyl, furanyl, pyrrolyl, isoxazolyl, pyrazolyl, imidazolyl, indolyl, benzothiophenyl, benzofuranyl, benzoxazolyl, benzothiazolyl, quinolyl, isoquinolyl, pyridyl and pyrimidinyl.

As more detailed exemplary Het1 radicals can be mentioned, for example, without being restricted thereto, thiophen-2-yl, thiophen-3-yl, furan-2-yl, furan-3-yl, 3-methyl-thiophen-2-yl, 4-methyl-thiophen-2-yl, 5-methyl-thiophen-2-yl, 5-ethyl-thiophen-2-yl, 4-methyl-furan-2-yl, 5-methyl-furan-2-yl, 5-phenyl-thiophen-2-yl, benzofuran-2-yl, benzothiophen-2-yl, benzothiophen-3-yl, benzoxazol-5-yl, benzthiazol-5-yl, 1-methyl-indol-5-yl, 1H-indol-2-yl, 1H-indol-3-yl, 1H-indol-4-yl, 1H-indol-5-yl, 1H-indol-6-yl, 6-trifluoromethyl-indol-2-yl, 7-trifluoromethyl-indol-2-yl, 5-methoxy-indol-2-yl, 1H-pyrrol-2-yl, pyrazol-4-yl, imidazol-4-yl, pyridin-2-yl, pyridin-3-yl, pyridin-4-yl, 4-methyl-pyridin-2-yl, 5-methyl-pyridin-2-yl, 6-methyl-pyridin-2-yl, 5-methyl-pyridin-3-yl, 2-methyl-pyridin-4-yl, 3-methyl-pyridin-4-yl, 6-methoxy-pyridin-2-yl, 2-methoxy-pyridin-3-yl, 4-methoxy-pyridin-3-yl, 5-methoxy-pyridin-3'-yl, 6-methoxy-pyridin-3-yl, pyrimidin-5-yl, 2-methoxy-pyrimidin-5-yl, quinolin-3-yl, quinolin-4-yl, quinolin-5-yl, quinolin-6-yl, quinolin-8-yl, isoquinolin-4-yl, isoquinolin-5-yl, 5-cyano-thiophen-2-yl, 5-carboxy-thiophen-2-yl, 3-carboxy-thiophen-2-yl, 5-dimethylamino-thiophen-2-yl, 2-acetyl-thiophen-3-yl, 5-acetyl-thiophen-2-yl, 3,5-dimethylisoxazol-4-yl, 4-chloro-thiophen-2-yl, 5-chloro-thiophen-2-yl, 3-fluoro-pyridin-4-yl, 3-chloro-pyridin-4-yl, 6-fluoro-pyridin-3-yl, 6-chloro-pyridin-3-yl, 2-fluoro-pyridin-3-yl, 2-chloro-pyridin-3-yl, 2-chloro-3-fluoro-pyridin-4-yl, 2-chloro-5-fluoro-pyridin-3-yl, 2,3-dichloro-pyridin-4-yl, 3,5-difluoro-pyridin-4-yl, 2,6-dichloro-pyridin-3-yl, 2-fluoro-6-methyl-pyridin-3-yl, 6-fluoro-2-methyl-pyridin-3-yl, 6-fluoro-5-methyl-pyridin-3-yl, 6-chloro-5-methyl-pyridin-3-yl, 2-chloro-6-methyl-pyridin-3-yl, 5,6-difluoro-indol-2-yl, or 5-chloro-indol-2-yl.

In a first special aspect (aspect a) of the present invention,

Het1 is optionally substituted by R3 and/or R4 and refers to a monocyclic or fused bicyclic 5- to 10-membered unsaturated or partially saturated heteroaryl radical comprising one to three heteroatoms, each of which is selected from a group consisting of nitrogen, oxygen and sulfur; or, particularly,

Het1 is optionally substituted by R3 and/or R4 and refers to a monocyclic or fused bicyclic 5- to 10-membered unsaturated heteroaryl (heteroaromatic) radical comprising one to three heteroatoms, each of which is selected from a group consisting of nitrogen, oxygen and sulfur;

In each case under the proviso that,

in a first subaspect of aspect a, Het1 is not pyridin-3-yl, and/or

in a second subaspect of aspect a, Het1 is not pyridyl, and/or

in a third subaspect of aspect a, Het1 is not pyridin-3-yl substituted by R5 wherein

R5 is halogen, 1-4C-alkyl or 1-4C-alkoxy, and/or

in a fourth subaspect of aspect a, Het1 is not pyridyl substituted by R5 wherein

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R5 is halogen, 1-4C-alkyl or 1-4C-alkoxy.

In a second special aspect (aspect b) of the present invention,

Het1 is optionally substituted by R3 and/or R4 and is a monocyclic 5-membered unsaturated heteroaryl (heteroaromatic) radical comprising one to three, particularly one or two, heteroatoms, each of which is selected from a group consisting of nitrogen, oxygen and sulfur.

In a third special aspect (aspect c) of the present invention,

Het1 is optionally substituted by R3 and/or R4 and is a monocyclic 6-membered unsaturated heteroaryl (heteroaromatic) radical comprising two nitrogen atoms.

In a fourth special aspect (aspect d) of the present invention,

Het1 is optionally substituted by R3 and/or R4 and is a fused bicyclic 9- or 10-membered unsaturated or partially saturated heteroaryl radical comprising one to three, particularly one or two, heteroatoms, each of which is selected from a group consisting of nitrogen, oxygen and sulfur.

In a fifth special aspect (aspect e) of the present invention,

Het1 is R3- and R4-substituted pyridyl,

In which

R3 is 1-4C-alkyl or halogen, and

R4 is 1-4C-alkyl or halogen,

or, in particular,

R3 is 1-4C-alkyl or halogen, and

R4 is halogen.

In a sixth special aspect (aspect f) of the present invention,

Het1 is optionally substituted by R3 and/or R4 and is a thiophenyl radical, in which

R3 is 1-4C-alkyl, chlorine, cyano, phenyl, dimethylamino, formyl, acetyl or carboxyl, and

R4 is 1-4C-alkyl,

or

Het1 is optionally substituted by R3 and is a furanyl radical, in which

R3 is 1-4C-alkyl,

or

Het1 is an indolyl, benzothiophenyl, benzofuranyl, benzoxazoyl, benzothiazoyl, quinolyl or isoquinolyl radical.

In a seventh special aspect (aspect g) of the present invention,

Het1 is optionally substituted by R3 and/or R4 and is a thiophenyl radical, in which

R3 is 1-4C-alkyl, chlorine, cyano or phenyl, and

R4 is 1-4C-alkyl,

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or

Het1 is optionally substituted by R3 and is a furanyl radical, in which  
 R3 is 1-4C-alkyl,

or

Het1 is an indolyl, benzothiophenyl, benzofuranyl, benzoxaloyl, benzothiazolyl, quinolyl or isoquinolyl radical.

In an eighth special aspect (aspect h) of the present invention,

Het1 is optionally substituted by R3 and/or R4 and is a thiophenyl radical, in which  
 R3 is methyl, chlorine, cyano or phenyl, and  
 R4 is methyl,

or

Het1 is optionally substituted by R3 and is a furanyl radical, in which  
 R3 is methyl,

or

Het1 is an indolyl radical.

In a ninth special aspect (aspect i) of the present invention;

Het1 radicals according to special aspect a may include, for example, R3- and R4-substituted pyridinyl; or may be optionally substituted by R3 and/or R4 and may include, without being restricted to, thiophenyl, furanyl, pyrrolyl, isoxazolyl, pyrazolyl, imidazolyl, indolyl, benzothiophenyl, benzofuranyl, benzoxaloyl, benzothiazolyl, quinolyl, isoquinolyl and pyrimidinyl.

In a tenth special aspect (aspect j) of the present invention,

as more detailed exemplary Het1 radicals according to special aspect a can be mentioned, for example, thiophen-2-yl, thiophen-3-yl, furan-2-yl, furan-3-yl, 3-methyl-thiophen-2-yl, 4-methyl-thiophen-2-yl, 5-methyl-thiophen-2-yl, 5-ethyl-thiophen-2-yl, 4-methyl-furan-2-yl, 5-methyl-furan-2-yl, 5-phenyl-thiophen-2-yl, benzofuran-2-yl, benzothiophen-2-yl, benzothiophen-3-yl, benzoxazol-5-yl, benzthiazol-5-yl, 1-methyl-indol-5-yl, 1H-indol-2-yl, 1H-indol-3-yl, 1H-indol-4-yl, 1H-indol-5-yl, 1H-indol-8-yl, 6-trifluoromethyl-indol-2-yl, 7-trifluoromethyl-indol-2-yl, 5-methoxy-indol-2-yl, 1H-pyrrol-2-yl, pyrazol-4-yl, imidazol-4-yl, pyrimidin-5-yl, 2-methoxy-pyrimidin-5-yl, quinolin-3-yl, quinolin-4-yl, quinolin-5-yl, quinolin-6-yl, quinolin-8-yl, isoquinolin-4-yl, isoquinolin-5-yl, 5-cyano-thiophen-2-yl, 5-carboxy-thiophen-2-yl, 3-carboxy-thiophen-2-yl, 5-dimethylamino-thiophen-2-yl, 2-acetyl-thiophen-3-yl, 5-acetyl-thiophen-2-yl, 3,5-dimethylisoxazol-4-yl, 4-chloro-thiophen-2-yl, 5-chloro-thiophen-2-yl, 2-chloro-3-fluoro-pyridin-4-yl, 2-chloro-5-fluoro-pyridin-3-yl, 2,3-dichloro-pyridin-4-yl, 3,5-difluoro-pyridin-4-yl, 2,6-dichloro-pyridin-3-yl, 2-fluoro-6-methyl-pyridin-3-yl, 6-fluoro-2-methyl-pyridin-3-yl, 6-fluoro-5-methyl-pyridin-3-yl, 6-chloro-5-methyl-pyridin-3-yl, 2-chloro-6-methyl-pyridin-3-yl, 5,6-difluoro-indol-2-yl, or 5-chloro-indol-2-yl.

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In an eleventh special aspect (aspect k) of the present invention, as more detailed exemplary Het1 radicals according to special aspect a can be mentioned, for example, thiophen-2-yl, thiophen-3-yl, furan-2-yl, furan-3-yl, benzofuran-2-yl, benzothiophen-2-yl, benzothiophen-3-yl, benzoxazol-5-yl, benzthiazol-5-yl, 1H-indol-2-yl, 1H-indol-3-yl, 1H-indol-4-yl, 1H-indol-5-yl, 1H-indol-8-yl, 1H-pyrrrol-2-yl, pyrazol-4-yl, imidazol-4-yl, pyrimidin-5-yl, quinolin-3-yl, quinolin-4-yl, quinolin-5-yl, quinolin-8-yl, isoquinolin-4-yl or isoquinolin-5-yl.

Suitable salts for compounds according to the invention - depending on substitution - are all acid addition salts or all salts with bases. Particular mention may be made of the pharmacologically tolerable inorganic and organic acids and bases customarily used in pharmacy. Those suitable are, on the one hand, water-insoluble and, particularly, water-soluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulphuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)benzoic acid, butyric acid, sulphosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulphonic acid, methanesulphonic acid or 3-hydroxy-2-naphthoic acid, the acids being employed in salt preparation - depending on whether a mono- or polybasic acid is concerned and depending on which salt is desired - in an equimolar quantitative ratio or one differing therefrom.

On the other hand, salts with bases are - depending on substitution - also suitable. As examples of salts with bases are mentioned the lithium, sodium, potassium, calcium, aluminium, magnesium, titanium, ammonium, meglumine or guanidinium salts, here, too, the bases being employed in salt preparation in an equimolar quantitative ratio or one differing therefrom.

Pharmacologically intolerable salts, which can be obtained, for example, as process products during the preparation of the compounds according to the invention on an industrial scale, are converted into pharmacologically tolerable salts by processes known to the person skilled in the art.

According to expert's knowledge the compounds of the invention as well as their salts may contain, e.g. when isolated in crystalline form, varying amounts of solvents. Included within the scope of the invention are therefore all solvates and in particular all hydrates of the compounds according to this invention as well as all solvates and in particular all hydrates of the salts of the compounds according to this invention.

A person skilled in the art knows on the base of his/her expert knowledge that the compounds according to this invention can exist, with regard to the fused imidazo ring, in different tautomeric forms such as e.g. in the 1-H form or, preferably, in the 3-H form, which is shown in formula I. The Invention includes all conceivable tautomers in pure form as well as in any mixing ratio. Particularly the present invention includes the pure 1-H- and, preferably, 3-H-tautomers as well as any mixtures thereof.

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An embodiment (embodiment a) according to this invention includes compounds of formula I, in which

- R1 is 1-4C-alkoxy, particularly methoxy,
- A is 1-4C-alkylene, particularly ethylene,
- R2 is halogen, 1-4C-alkyl, 1-4C-alkoxy or, particularly, hydrogen,
- Het1 is optionally substituted by R3 and/or R4 and is a monocyclic or fused bicyclic 5- to 10-membered unsaturated or partially saturated heteroaryl radical comprising one to three heteroatoms, each of which is selected from a group consisting of nitrogen, oxygen and sulfur, in which
- R3 is 1-4C-alkyl, halogen, cyano, trifluoromethyl, phenyl, mono- or di-1-4C-alkylamino, formyl, 1-4C-alkylcarbonyl, carboxyl or 1-4C-alkoxy,
- R4 is 1-4C-alkyl or halogen,

under the proviso that 2-[2-(4-methoxypyridin-2-yl)ethyl]-6-(pyridin-3-yl)-3H-imidazo-[4,5-b]pyridine is thereof disclaimed,

as well as the salts, N-oxides and the salts of the N-oxides of these compounds.

Compounds according to embodiment a more worthy to be mentioned are those compounds of formula I,

in which

- R1 is methoxy,
- A is ethylene,
- R2 is hydrogen,
- Het1 is optionally substituted by R3 and/or R4 and is a thiophenyl radical, in which
- R3 is 1-4C-alkyl, chlorine, cyano, phenyl, dimethylamino, formyl, acetyl or carboxyl, and
- R4 is 1-4C-alkyl,
- or
- Het1 is optionally substituted by R3 and is a furanyl radical, in which
- R3 is 1-4C-alkyl,
- or
- Het1 is optionally substituted by R3 and/or R4 and is a pyridyl radical, in which
- R3 is 1-4C-alkyl, chlorine, fluorine, 1-4C-alkoxy or carboxyl, and
- R4 is 1-4C-alkyl or chlorine,
- or
- Het1 is an indolyl, benzothiophenyl, benzofuranyl, benzoxaloyl, benzothiazolyl, quinolyl or isoquinolyl radical,

under the proviso that 2-[2-(4-methoxypyridin-2-yl)ethyl]-6-(pyridin-3-yl)-3H-imidazo-[4,5-b]pyridine is thereof disclaimed,

as well as the salts, N-oxides and the salts of the N-oxides of these compounds.

Compounds according to embodiment a in particular worthy to be mentioned are those compounds of formula I,

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in which

R1 is methoxy,

A is ethylene,

R2 is hydrogen,

Het1 is optionally substituted by R3 and/or R4 and is a thiophenyl radical, in which

R3 is 1-4C-alkyl, chlorine, cyano or phenyl, and

R4 is 1-4C-alkyl,

or

Het1 is optionally substituted by R3 and is a furanyl radical, in which

R3 is 1-4C-alkyl,

or

Het1 is optionally substituted by R3 and/or R4 and is a pyridyl radical, in which

R3 is 1-4C-alkyl, chlorine, fluorine or 1-4C-alkoxy, and

R4 is 1-4C-alkyl or chlorine,

or

Het1 is an indolyl, benzothiophenyl, benzofuranyl, benzoxaloyl, benzothiazolyl, quinolyl or isoquinolyl radical,

under the proviso that 2-[2-(4-methoxypyridin-2-yl)ethyl]-6-(pyridin-3-yl)-3H-imidazo-[4,5-b]pyridine is thereof disclaimed,

as well as the salts, N-oxides and the salts of the N-oxides of these compounds.

Compounds according to embodiment a in more particular worthy to be mentioned are those compounds of formula I.

in which

R1 is methoxy,

A is ethylene,

R2 is hydrogen,

Het1 is optionally substituted by R3 and/or R4 and is a thiophenyl radical, in which

R3 is methyl, chlorine, cyano or phenyl, and

R4 is methyl,

or

Het1 is optionally substituted by R3 and is a furanyl radical, in which

R3 is methyl,

or

Het1 is optionally substituted by R3 and/or R4 and is a pyridyl radical, in which

R3 is methyl, chlorine, fluorine or methoxy, and

R4 is methyl or chlorine,

or

Het1 is an indolyl radical,

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under the proviso that 2-[2-(4-methoxypyridin-2-yl)ethyl]-6-(pyridin-3-yl)-3H-imidazo-[4,5-b]pyridine is thereof disclaimed,

as well as the salts, N-oxides and the salts of the N-oxides of these compounds.

Compounds according to embodiment a to be emphasized are those compounds of formula I, in which

R1 is methoxy,

A is ethylene,

R2 is hydrogen,

Het1 is a thiophenyl, furanyl, pyridyl or indolyl radical,

under the proviso that 2-[2-(4-methoxypyridin-2-yl)ethyl]-6-(pyridin-3-yl)-3H-imidazo-[4,5-b]pyridine is thereof disclaimed,

as well as the salts, N-oxides and the salts of the N-oxides of these compounds.

A further embodiment (embodiment b) according to this invention includes compounds of formula I, in which

R1 is 1-4C-alkoxy, particularly methoxy,

A is 1-4C-alkylene, particularly ethylene,

R2 is halogen, 1-4C-alkyl, 1-4C-alkoxy or, particularly, hydrogen,

Het1 is optionally substituted by R3 and/or R4 and is a monocyclic or fused bicyclic 5- to 10-membered unsaturated or partially saturated heteroaryl radical comprising one to three heteroatoms, each of which is selected from a group consisting of nitrogen, oxygen and sulfur, in which

R3 is 1-4C-alkyl, halogen, cyano, trifluoromethyl, phenyl, mono- or di-1-4C-alkylamino, formyl, 1-4C-alkylcarbonyl, carboxyl or 1-4C-alkoxy,

R4 is 1-4C-alkyl or halogen,

under the proviso that

Het1 is not pyridyl, and

Het1 is not pyridyl substituted by R5 wherein

R5 is halogen, 1-4C-alkyl or 1-4C-alkoxy,

as well as the salts, N-oxides and the salts of the N-oxides of these compounds.

A further embodiment (embodiment c) according to this invention includes compounds of formula I, in which

R1 is 1-4C-alkoxy, particularly methoxy,

A is 1-4C-alkylene, particularly ethylene,

R2 is halogen, 1-4C-alkyl, 1-4C-alkoxy or, particularly, hydrogen;

Het1 is optionally substituted by R3 and/or R4 and is a monocyclic 5-membered unsaturated heteroaryl (heteroaromatic) radical comprising one to three, particularly one or two, heteroatoms, each of which is selected from a group consisting of nitrogen, oxygen and sulfur,

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or

Het1 is optionally substituted by R3 and/or R4 and is a monocyclic 6-membered unsaturated heteroaryl (heteroaromatic) radical comprising two nitrogen atoms,

or

Het1 is optionally substituted by R3 and/or R4 and is a fused bicyclic 9- or 10-membered unsaturated or partially saturated heteroaryl radical comprising one to three, particularly one or two, heteroatoms, each of which is selected from a group consisting of nitrogen, oxygen and sulfur, in which

R3 is 1-4C-alkyl, halogen, cyano, trifluoromethyl, phenyl, mono- or di-1-4C-alkylamino, formyl, 1-4C-alkylcarbonyl, carboxyl or 1-4C-alkoxy, and

R4 is 1-4C-alkyl or halogen;

or

Het is R3- and R4-substituted pyridyl,

in which

R3 is 1-4C-alkyl or halogen, and

R4 is 1-4C-alkyl or halogen,

or, in particular,

R3 is 1-4C-alkyl or halogen, and

R4 is halogen;

as well as the salts, N-oxides and the salts of the N-oxides of these compounds.

Compounds according to embodiment c worthy to be mentioned are those compounds of formula I,

in which

R1 is methoxy,

A is ethylene,

R2 is hydrogen,

Het1 is optionally substituted by R3 and/or R4 and is a thiophenyl radical, in which

R3 is 1-4C-alkyl, chlorine, cyano, phenyl, dimethylamino, formyl, acetyl or carboxyl, and

R4 is 1-4C-alkyl,

or

Het1 is optionally substituted by R3 and is a furanyl radical, in which

R3 is 1-4C-alkyl,

or

Het is a R3- and R4-substituted pyridyl radical, in which

R3 is 1-4C-alkyl, chlorine or fluorine, and

R4 is chlorine,

or

Het1 is an indolyl, benzothiophenyl, benzofuranyl, benzoxazolyl, benzothiazolyl, quinolyl or isoquinolyl radical,

as well as the salts, N-oxides and the salts of the N-oxides of these compounds.

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**Compounds according to embodiment c more worthy to be mentioned are those compounds of formula I,**

**In which**

R1 is methoxy,

A is ethylene,

R2 is hydrogen,

Het1 is optionally substituted by R3 and/or R4 and is a thiophenyl radical, in which

R3 is 1-4C-alkyl, chlorine, cyano or phenyl, and

R4 is 1-4C-alkyl,

or

Het1 is optionally substituted by R3 and is a furanyl radical, in which

R3 is 1-4C-alkyl,

or

Het is a R3- and R4-substituted pyridyl radical, in which

R3 is 1-4C-alkyl, chlorine or fluorine, and

R4 is chlorine,

or

Het1 is an indolyl, benzothiophenyl, benzofuranyl, benzoxaloyl, benzothiazolyl, quinolyl or isoquinolyl radical,

as well as the salts, N-oxides and the salts of the N-oxides of these compounds.

**Compounds according to embodiment c in particular worthy to be mentioned are those compounds of formula I,**

**In which**

R1 is methoxy,

A is ethylene,

R2 is hydrogen,

Het1 is optionally substituted by R3 and/or R4 and is a thiophenyl radical, in which

R3 is methyl, chlorine, cyano or phenyl, and

R4 is methyl,

or

Het1 is optionally substituted by R3 and is a furanyl radical, in which

R3 is methyl,

or

Het1 is an indolyl, benzothiophenyl, benzofuranyl, benzoxaloyl, benzothiazolyl, quinolyl or isoquinolyl radical,

as well as the salts, N-oxides and the salts of the N-oxides of these compounds.

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Compounds according to embodiment c in more particular worthy to be mentioned are those compounds of formula I,

in which

R1 is methoxy,

A is ethylene,

R2 is hydrogen,

Het1 is optionally substituted by R3 and/or R4 and is a thiophenyl radical, in which

R3 is methyl, chlorine, cyano or phenyl, and

R4 is methyl,

or

Het1 is optionally substituted by R3 and is a furanyl radical, in which

R3 is methyl,

or,

Het1 is an indolyl radical,

as well as the salts, N-oxides and the salts of the N-oxides of these compounds.

Compounds according to embodiment c to be emphasized are those compounds of formula I,

in which

R1 is methoxy,

A is ethylene,

R2 is hydrogen,

Het1 is a thiophenyl, furanyl or indolyl radical,

as well as the salts, N-oxides and the salts of the N-oxides of these compounds.

A special embodiment of the compounds of the present invention include those compounds of formula I in which R1 is methoxy.

Another special embodiment of the compounds of the present invention include those compounds of formula I in which A is ethylene.

Another special embodiment of the compounds of the present invention include those compounds of formula I in which R2 is hydrogen.

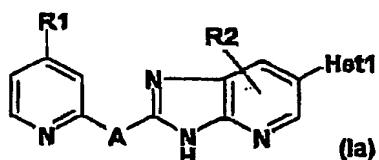
Another special embodiment of the compounds of the present invention include those compounds of formula I in which R1 is methoxy and A is ethylene.

Another special embodiment of the compounds of the present invention include those compounds of formula I in which R1 is methoxy and A is ethylene and R2 is hydrogen.

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Another special embodiment of the compounds of the present invention include compounds of formula Ia



In which the moiety Het1 is bonded to the 6-position of the imidazopyridine ring.

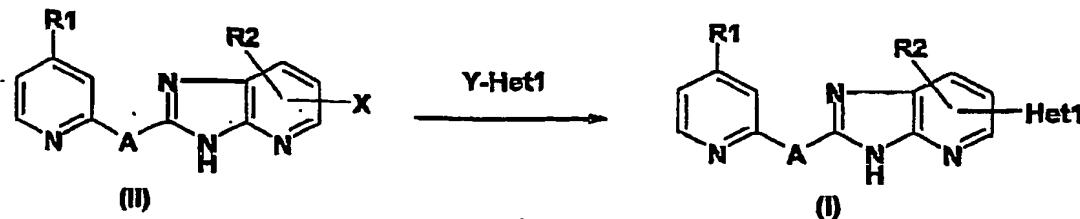
Another special embodiment of the compounds of the present invention include those compounds of formula I in which R1 is methoxy, A is ethylene, R2 is hydrogen, and Het1 is bonded to the 6-position of the imidazopyridine ring.

Another special embodiment of the compounds of the present invention include those compounds of formula I in which R1 is methoxy, A is ethylene, R2 is hydrogen, and Het1 is bonded to the 6-position of the imidazopyridine ring and is pyridin-4-yl, pyridin-2-yl, 3-fluoro-pyridin-4-yl, 3-chloro-pyridin-4-yl, 6-fluoro-pyridin-3-yl, 6-chloro-pyridin-3-yl, 2-fluoro-pyridin-3-yl, 2-chloro-pyridin-3-yl, 4-methyl-pyridin-2-yl, 5-methyl-pyridin-2-yl, 6-methyl-pyridin-2-yl, 5-methyl-pyridin-3-yl, 2-methyl-pyridin-4-yl, 3-methyl-pyridin-4-yl, 8-methoxy-pyridin-2-yl, 2-methoxy-pyridin-3-yl, 4-methoxy-pyridin-3-yl, 5-methoxy-pyridin-3-yl or 6-methoxy-pyridin-3-yl.

Compounds of formula I can be obtained as described below and shown in the following reaction schemes, or as specified by way of example in the following examples or similarly or analogously thereto.

Thus, as shown in reaction scheme 1 below, a compound of formula II, in which R1, R2 and A have the meanings given above and X is a suitable leaving group, preferably bromine or, particularly, iodine, is reacted with boronic acid esters (e.g. pinacol esters) or, particularly, boronic acids of formula Y-Het1, in which Het1 has the meanings given above and Y is a boronic acid group or a boronic acid ester group, under conditions appropriate for a Suzuki reaction to occur to give compounds of formula I, in which R1, R2, A and Het1 have the meanings mentioned above.

### **Reaction Scheme 1:**



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In more detail, the Suzuki reaction mentioned can be carried out in organic solvents alone, for example in toluene, benzene, dimethylformamide or in ethereal (e.g. dimethoxyethane or, in particular, dioxane) or alcohol solvents or in a mixture thereof, or preferably in a mixture comprising an organic solvent (in particular dioxane) and water, with organic (e.g. triethylamine) or preferably inorganic base (e.g. potassium hydroxide, thallium hydroxide, sodium bicarbonate, cesium carbonate, cesium fluoride or, in particular, potassium carbonate) in the presence of a transition metal catalyst, for example, a nickel or, in particular, palladium catalyst (e.g.  $Pd(OAc)_2$ ,  $PdCl_2(PPPh_3)_2$  or, in particular,  $Pd(PPPh_3)_4$ ), and, optionally, lithium chloride. The reaction is carried out at a temperature in the range from 20° to 160°C, usually 60° to 130°C for 10 minutes to 5 days, usually 30 minutes to 24 hours. Advantageously, the solvents used are degassed and the reaction is carried out under protective gas.

The Suzuki reaction is for example described in Tetrahedron Lett. 1998, 39, 4467, J. Org. Chem. 1999, 64, 1372 or Heterocycles 1992, 34, 1395. A general review of Suzuki cross-couplings between boronic acids and aryl halides can be found in Miyaura, N; Suzuki, A. Chem. Rev. 1995, 95, 2457.

Boronic acids or boronic acid esters of formula Y-Het1, in which Y and Het1 have the meanings given above, are known, e.g. commercially available, or can be obtained in an art-known manner or analogously or similarly to known compounds.

Compounds of formula II, in which R1, R2, X and A have the meanings given above, can be obtained as exemplarily described in the following examples and/or shown in the following reaction scheme 2 or similarly or analogously thereto.

In the following reaction scheme the synthesis of compounds of formula II, in which R1, R2 and X have the meanings given above and A is ethylene, is exemplarily described.

The carbon chain in 2-position of the compounds of formula VII is lengthened, for example, by a condensation (with a malonic acid derivative) and a subsequent hydrogenation reaction. Alternatively, the carbon chain can be lengthened using a Wittig reaction followed by a hydrogenation reaction.

The methyl 3-(4-(1-4C)-alkoxypyridin-2-yl)propionate (compound of formula V) or the corresponding acid (compound of formula IV) are converted with a 2,3-diaminopyridine derivative (compound of formula III) to give desired compounds of formula II.

The synthesis of 4-methoxy-pyridin-2-carbaldehyde (compound of formula VII) is described for example in Ashimori et al, Chem Pharm Bull 38, 2446-2458 (1990).

Compounds of formula VII can be also prepared starting from commercially available 4-nitro-2-picoline-N-oxide by exchange of the nitro group by an 1-4C-alkoxy group. The resulting 4-(1-4C)-alkoxy-2-

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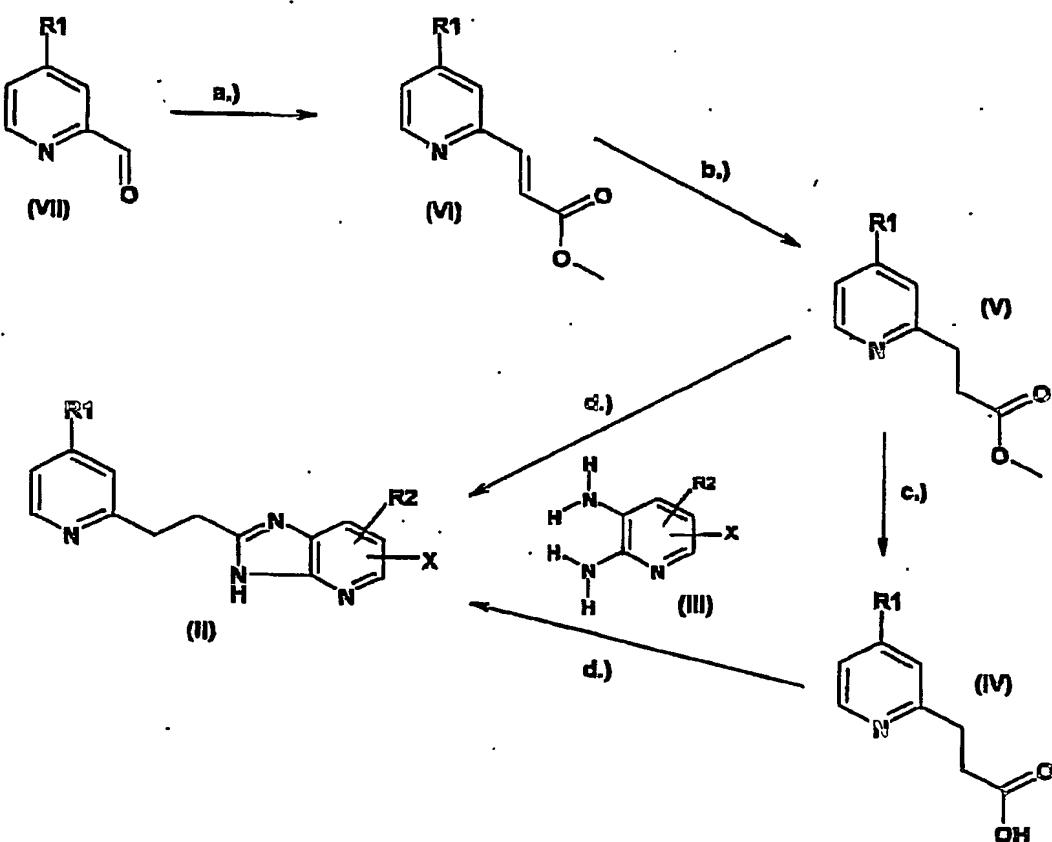
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picoline-N-oxide is then via a rearrangement and an oxidation step converted to 4-(1-4C)-alkoxy-pyridin-2-carbaldehyd (compound of formula VII).

The synthesis of 3-(4-methoxypyridin-2-yl)propionic acid (compound of formula IV) is described in the paragraph Starting Compounds.

Compounds of formula III, in which R<sub>2</sub> and X have the meanings indicated above are known or can be prepared in a known manner or analogously or similarly to art-known compounds.

#### Reaction Scheme 2:



a.) Monomethyl malonate potassium salt/piperidine/pyridine

b.) H<sub>2</sub>/Pd/C (10%)

c.) NaOH

d.)

d.) Polyphosphoric acid

The compounds of formula I according to this invention can be converted, optionally, into their N-oxides, for example with the aid of hydrogen peroxide in methanol or with the aid of m-chloroperoxybenzoic acid in dichloromethane (e.g. in an analogous or similar manner as described exemplarily in the following examples). The person skilled in the art is familiar on the basis of his/her

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expert knowledge with the reaction conditions which are specifically necessary for carrying out the N-oxidation.

It is known to the person skilled in the art that if there are a number of reactive centers on a starting or intermediate compound it may be necessary to block one or more reactive centers temporarily by protective groups in order to allow a reaction to proceed specifically at the desired reaction center. A detailed description for the use of a large number of proven protective groups is found, for example, in T.W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, 1999, 3<sup>rd</sup> Ed, or in P. Kocienski, Protecting Groups, Thieme Medical Publishers, 2000.

The substances according to the invention are isolated and purified in a manner known per se, e.g. by distilling off the solvent *in vacuo* and recrystallizing the residue obtained from a suitable solvent or subjecting it to one of the customary purification methods, such as column chromatography on a suitable support material.

Salts are obtained by dissolving the free compound in a suitable solvent (for example a ketone like acetone, methylethylketone, or methylisobutylketone, an ether, like diethyl ether, tetrahydrofuran or dioxane, a chlorinated hydrocarbon, such as methylene chloride or chloroform, or a low molecular weight aliphatic alcohol, such as ethanol, isopropanol) which contains the desired acid, or to which the desired acid is then added. The salts are obtained by filtering, reprecipitating, precipitating with a non-solvent for the addition salt or by evaporating the solvent. Salts obtained can be converted by basification into the free compounds which, in turn, can be converted into salts. In this manner, pharmacologically non-tolerable salts can be converted into pharmacologically tolerable salts.

Suitably, the conversions mentioned in this invention can be carried out analogously or similarly to methods which are familiar per se to the person skilled in the art, for example, in the manner which is described by way of example in the following examples.

The person skilled in the art knows on the basis of his/her knowledge and on the basis of those synthesis routes, which are shown and described within the description of this invention, how to find other possible synthesis routes for compounds according to this invention. All these other possible synthesis routes are also part of this invention.

Having described the invention in detail, the scope of the present invention is not limited only to those described characteristics or embodiments. As will be apparent to persons skilled in the art, modifications, analogies, variations, derivations, homologisations and adaptations to the described invention can be made on the base of art-known knowledge and/or, particularly, on the base of the disclosure (e.g. the explicit, implicit or inherent disclosure) of the present invention without departing from the spirit and scope of this invention.

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The following examples illustrate the invention in greater detail, without restricting it. As well, further compounds according to the present invention of which the preparation is explicitly not described, can be prepared in an analogous way or in a way which is known by a person skilled in the art using customary preparation methods and process techniques.

The compounds, which are mentioned in the examples as well as their salts are a preferred subject of the Invention.

**1226EPORD01 2003-09 05****- 18 -****Examples****Final products****1. 6-Furan-2-yl-[2-(4-methoxypyridin-2-yl)ethyl]-3H-imidazo[4,5-b]pyridine**

0.76 g of 2-[2-(4-methoxypyridin-2-yl)ethyl]-6-iodo-3H-imidazo[4,5-b]pyridine (starting material A1) and 0.45 g of 2-furanylboronic acid are dissolved in 30 ml degassed dioxane. Then a solution of 0.55 g of potassium carbonate and 0.17 g of lithium chloride in 26 ml of degassed water and 0.23 g of tetrakis(triphenylphosphine)palladium(0) are added. The mixture is heated to reflux under N<sub>2</sub> for 24 hours and, after cooling, addition of water and adjusting the pH to 7, it is extracted three times with dichloromethane. The combined organic phases are dried over sodium sulfate, concentrated and the residue is dissolved in hot toluene. After cooling and addition of a small volume of diethylether, the formed precipitate is isolated and dried in vacuo. This gives 0.445 g of the title compound of m.p. 147-148°C. The mass spectrum shows the molecular peak MH<sup>+</sup> at 321.3 Da.

**2. 6-Furan-3-yl-[2-(4-methoxypyridin-2-yl)ethyl]-3H-imidazo[4,5-b]pyridine**

0.57 g of 2-[2-(4-methoxypyridin-2-yl)ethyl]-6-iodo-3H-imidazo[4,5-b]pyridine (starting material A1) and 0.25 g of 3-furanylboronic acid are dissolved in 12 ml degassed dioxane. Then a solution of 0.415 g of potassium carbonate and 0.13 g of lithium chloride in 8 ml of degassed water and 0.17 g of tetrakis(triphenylphosphine)palladium(0) are added. The mixture is heated to reflux under N<sub>2</sub> for 20 hours and, after cooling, addition of water and adjusting the pH to 7, it is extracted three times with dichloromethane. The combined organic phases are dried over sodium sulfate, concentrated and the residue is crystallized from hot toluene. This gives 0.35 g of the title compound of m.p. 193-194°C. The mass spectrum shows the molecular peak MH<sup>+</sup> at 321.3 Da.

**3. 2-[2-(4-Methoxypyridin-2-yl)ethyl]-6-(pyridin-4-yl)-3H-imidazo-[4,5-b]pyridine**

0.38 g of 2-[2-(4-methoxypyridin-2-yl)ethyl]-6-iodo-3H-imidazo[4,5-b]pyridine (starting material A1) and 0.31 g of 2-(4-pyridyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane are dissolved in 5 ml of degassed dioxane. Then a solution of 0.276 g of potassium carbonate and 0.085 g of lithium chloride in 5 ml degassed water and 0.115 g of tetrakis(triphenylphosphine)palladium(0) are added. The mixture is heated to reflux under N<sub>2</sub> for 24 hours and, after cooling and addition of water, it is extracted three times with dichloromethane. The combined organic phases are dried over sodium sulfate, concentrated and the residue is chromatographed on a silica gel column (dichloromethane/methanol 25:15:1 + 1% NH<sub>4</sub>OH). Concentration of the chromatographically pure fractions and crystallization from acetonitril

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gives 0.16 g of the title compound of m.p. 237-238°C. The mass spectrum shows the molecular peak  $\text{MH}^+$  at 332.3Da.

**4. 2-[2-(4-Methoxypyridin-2-yl)ethyl]-6-(thiophen-2-yl)-3H-imidazo-[4,5-b]pyridine**

0.38 g of 2-[2-(4-methoxypyridin-2-yl)ethyl]-6-iodo-3H-imidazo[4,5-b]pyridine (starting material A1) and 0.192 g of 2-thiophenboronic acid are dissolved in 16 ml degassed dioxane. Then a solution of 0.276 g of potassium carbonate and 0.85 g of lithium chloride in 13 ml of degassed water and 0.115 g of tetrakis(triphenylphosphine)palladium(0) are added. The mixture is heated to reflux under  $\text{N}_2$  for 18 hours and, after cooling, addition of water and adjusting the pH to 7, it is extracted three times with dichloromethane. The combined organic phases are dried over sodium sulfate, concentrated and the residue is crystallized from ethylacetate/acetonitril (2:1) and finally from 1-propanol. This gives 0.185 g of the title compound of m.p. 132-133°C. The mass spectrum shows the molecular peak  $\text{MH}^+$  at 337.3 Da.

**5. 2-[2-(4-Methoxypyridin-2-yl)ethyl]-6-(thiophen-3-yl)-3H-imidazo-[4,5-b]pyridine**

0.38 g of 2-[2-(4-methoxypyridin-2-yl)ethyl]-6-iodo-3H-imidazo[4,5-b]pyridine (starting material A1) and 0.192 g of 3-thiophenboronic acid are dissolved in 16 ml degassed dioxane. Then a solution of 0.276 g of potassium carbonate and 0.85 g of lithium chloride in 13 ml of degassed water and 0.115 g of tetrakis(triphenylphosphine)palladium(0) are added. The mixture is heated to reflux under  $\text{N}_2$  for 18 hours and, after cooling, addition of water and adjusting the pH to 7, it is extracted three times with dichloromethane. The combined organic phases are dried over sodium sulfate, concentrated and the residue is crystallized from 1-propanol. This gives 0.205 g of the title compound of m.p. 154-155°C. The mass spectrum shows the molecular peak  $\text{MH}^+$  at 337.3 Da.

**6. 5-(1H-Indol-5-yl)-2-[2-(4-methoxypyridin-2-yl)ethyl]-3H-imidazo-[4,5-b]pyridine**

0.78 g of 2-[2-(4-methoxypyridin-2-yl)ethyl]-6-iodo-3H-imidazo[4,5-b]pyridine (starting material A1) and 0.483 g of 5-indolboronic acid are dissolved in 13 ml of degassed dioxane. Then a solution of 0.55 g of potassium carbonate and 0.17 g of lithium chloride in 13 ml of degassed water and 0.23 g of tetrakis(triphenylphosphine)palladium(0) are added. The mixture is heated to reflux under  $\text{N}_2$  for 24 hours and, after cooling and addition of water, it is extracted three times with dichloromethane. The combined organic phases are dried over sodium sulfate, concentrated and the residue is chromatographed on a silica gel column (dichloromethane/methanol 25-15:1). Concentration of the

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chromatographically pure fractions and crystallization from ethyl acetate gives 0.55 g of the title compound of m.p. 241-242°C. The mass spectrum shows the molecular peak  $MH^+$  at 370.3 Da.

**Starting materials:****A1. 2-[2-(4-Methoxypyridin-2-yl)ethyl]-5-iodo-3H-imidazo[4,5-b]pyridine**

With stirring, a mixture of 8.06 g of 3-(4-methoxypyridin-2-yl)propionic acid (starting material B1), 9.5 g of 2,3-diamino-5-iodopyridine (Cugola et al., Bioorg.Med. Chem.Lett. 22, 2749-2754 (1996)) and 150 g of polyphosphoric acid (PPA) is heated at 140°C for 22 hours. After cooling, the mixture is poured into about 1000 ml of ice-water and then neutralized (pH 7-8) using 6N aqueous sodium hydroxide solution. The mixture is extracted four times with ethyl acetate and the combined organic phases are evaporated to dryness. The residue is crystallized first from ethyl acetate and then from methanol, giving 9.4 g of the title compound as a light-beige powder of m.p. 207-208°C; the mass spectrum shows the molecular peak  $MH^+$  at 381.2 Da.

**B1. 3-(4-Methoxypyridin-2-yl)propionic acid**

41.95 g of methyl 3-(4-methoxypyridin-2-yl)propionate (starting material C1) are dissolved in 700 ml of tetrahydrofuran, and 217 ml of 1N sodium hydroxide solution are added. The mixture is stirred at RT until no more starting material is detectable (TLC). The mixture is neutralized using 217 ml of 1N hydrochloric acid solution, evaporated to dryness and dried under high vacuum. The colorless residue is ground and extracted four times with dichloromethane/methanol (9:1). The combined extracts are evaporated to dryness. This gives 33.2 g of the title compound as a colorless powder of m.p. 131-132°C. The mass spectrum shows the molecular peak  $MH^+$  at 182 Da.

**C1. Methyl 3-(4-methoxypyridin-2-yl)propionate**

43.1 g of methyl 3-(4-methoxypyridin-2-yl)acrylate (starting material D1) in 600 ml of methanol are hydrogenated over 3.0 g of Pd/C (10% strength) until the starting material has disappeared (TLC). The catalyst is filtered off, and the mixture is then concentrated and dried under high vacuum. This gives 41.95 g of the title compound as a light-yellow oil. The mass spectrum shows the molecular peak  $MH^+$  at 196 Da.

**D1. Methyl 3-(4-methoxypyridin-2-yl)acrylate**

A mixture of 45 g of 4-methoxypyridine-2-carbaldehyde (Ashimori et al., Chem.Pharm.Bull. 38, 2448-2458 (1990)), 75.80 g of pyridine hydrochloride, 102.45 g of monomethyl malonate potassium salt and

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4.1 ml of piperidine in 700 ml of pyridine are slowly heated, with stirring, to 120°C. When the evolution of gas starts, the heating source is temporarily removed to stop the reaction from becoming too violent. Once the reaction has subsided, the mixture is stirred at 120°C for a further 2.5 hours, and the pyridine is then distilled off under reduced pressure. The residue is partitioned between ethyl acetate/water and the organic phase is washed with water and dried. The residue obtained after concentration is chromatographed on a silica gel column using ethyl acetate/petroleum ether 2:1. This initially gives 43.2 g of the title compound as a yellow oil which crystallizes on standing and then shows a m.p. of 80-82°C. The mass spectrum shows the molecular peak  $MH^+$  at 194 Da.

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Commercial applicability

The compounds according to the invention have valuable pharmacological properties which make them commercially utilizable. They are selective inhibitors of the enzyme inducible nitric oxide synthase. Nitric oxide synthases (NO-synthases, NOSs) are enzymes that generate NO and citrulline from the amino acid arginine. In certain pathophysiological situations such as arginine depletion or tetrahydrobiopterin depletion the generation of O<sub>2</sub><sup>-</sup> from NO-synthases instead or together with NO has been reported. NO is long known as a signalling molecule in most living organisms including mammals and humans. The most prominent action of NO is its smooth muscle relaxing activity, which is caused on the molecular level by the activation of soluble guanylate cyclase. In the last years a lot of other enzymes have been shown to be regulated by NO or reaction products of NO.

There exist three isoforms of NO-synthases which fall into two classes and differ in their physiologic functions and molecular properties. The first class, known as constitutive NO-synthases, comprises of the endothelial NO-synthase and the neuronal NO-synthase. Both isoenzymes are expressed constitutively in various cell types, but are most prominent in endothelial cells of blood vessel walls (therefore called endothelial NO-synthase, eNOS or NOS-III) and in neuronal cells (therefore called neuronal NO-synthase, nNOS or NOS-I). Activation of these two enzymes is dependent on Ca<sup>2+</sup>/Calmodulin which is generated by transient increases of the intracellular free Ca<sup>2+</sup> concentration. Activation of constitutive isoforms leads to transient bursts of nitric oxide resulting in nanomolar cellular or tissue NO concentrations. The endothelial isoform is involved in the physiologic regulation of blood pressure. NO generated by the neuronal isoform seems to have neurotransmitter function and the neuronal isoform is among other regulatory processes involved in memory function (long term potentiation).

In contrast to the constitutive isoforms the activation of inducible NO-synthase (iNOS, NOS-II), the sole member of the second class, is performed by transcriptional activation of the iNOS-promoter.

Proinflammatory stimuli lead to transcription of the gene for inducible NO-synthase, which is catalytically active without increases in the intracellular Ca<sup>2+</sup>-concentration. Due to the long half life of the inducible NO-synthase and the unregulated activity of the enzyme, high micromolar concentrations of NO are generated over longer time periods. These high NO-concentrations alone or in cooperation with other reactive radicals such as O<sub>2</sub><sup>-</sup> are cytotoxic. Therefore, in situations of microbial infections, iNOS is involved in cell killing by macrophages and other immune cells during early nonspecific immune responses.

There are a number of pathophysiological situations which among others are characterized by the high expression of Inducible NO-synthase and concomitant high NO or O<sub>2</sub><sup>-</sup> concentrations. It has been shown that these high NO concentrations alone or in combination with other radical species lead to tissue and organ damage and are causally involved in these pathophysiologies. As inflammation is characterized by the expression of proinflammatory enzymes, including Inducible NO-synthase, acute and chronic inflammatory processes are promising diseases for the therapeutic application of

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selective inhibitors of inducible NO-synthase. Other pathophysiologies with high NO-production from inducible NO-synthase are several forms of shock (septic, hemorrhagic and cytokine-induced). It is clear that nonselective NO-synthase inhibitors will lead to cardiovascular and neuronal side effects due to concomitant inhibition of constitutive NO-synthase isoforms.

It has been shown in in-vivo animal models of septic shock that reduction of circulating plasma NO-levels by NO-scavenger or inhibition of inducible NO-synthase restores systemic blood pressure, reduces organ damage and increases survival (deAngelo Exp. Opin. Pharmacother. 19-29, 1999; Redl et al. Shock 8, Suppl. 51, 1997; Strand et al. Crit.Care Med. 26, 1490-1499, 1998). It has also been shown that increased NO production during septic shock contributes to cardiac depression and myocardial dysfunction (Sun et al. J. Mol.Cell Cardiol. 30, 989-997, 1998). Furthermore there are also reports showing reduced infarct size after occlusion of the left anterior coronary artery in the presence of NO-synthase inhibitors (Wang et al. Am. J. Hypertens. 12, 174-182, 1999). Considerable inducible NO-synthase activity is found in human cardiomyopathy and myocarditis, supporting the hypothesis that NO accounts at least in part for the dilatation and impaired contractility in these pathophysiologies (de Belder et al. Br. Heart. J. 4, 426-430, 1995).

In animal models of acute or chronic inflammation, blockade of inducible NO-synthase by isoform-selective or nonselective inhibitors or genetic knock out improves therapeutic outcome. It is reported that experimental arthritis (Connor et al. Eur. J. Pharmacol. 273, 15-24, 1995) and osteoarthritis (Pelletier et al. Arthritis & Rheum. 41, 1275-1286, 1998), experimental inflammations of the gastro-Intestinal tract (Zingarelli et al. Gut 45, 199-209, 1999), experimental glomerulonephritis (Narita et al. Lab. Invest. 72, 17-24, 1995), experimental diabetes (Corbett et al. PNAS 90, 8992-8995, 1993), LPS-induced experimental lung injury is reduced by inhibition of inducible NO-synthase or in iNOS-knock out mice (Kristof et al. Am. J. Crit. Care. Med. 158, 1883-1889, 1998). A pathophysiological role of inducible NO-synthase derived NO or O<sub>2</sub><sup>-</sup> is also discussed in chronic inflammatory diseases such as asthma, bronchitis and COPD.

Furthermore, in models of neurodegenerative diseases of the CNS such as MPTP-induced parkinsonism, amyloid peptide induced Alzheimer's disease (Ishii et al., FASEB J. 14, 1485-1489, 2000), malonate induced Huntington's disease (Connor et al. Neuropharmacol. 35, 459-465, 1996), experimental meningitis (Korytko & Boje Neuropharmacol. 35, 231-237, 1996) and experimental encephalitis (Parkinson et al. J. Mol. Med. 75, 174-186, 1997) a causal participation of NO and inducible NO-synthase has been shown.

Increased iNOS expression has been found in the brains of AIDS victims and it is reasonable to assume a role of iNOS in AIDS related dementia (Bagasra et al. J. Neurovirol. 3 153-167, 1997).

Other studies implicated nitric oxide as a potential mediator of microglia dependent primary demyelination, a hallmark of multiple sclerosis (Parkinson et al. J. Mol. Med. 75, 174-186, 1997).

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An inflammatory reaction with concomitant expression of inducible NO-synthase also takes place during cerebral ischemia and reperfusion (Iadecola et al. Stroke 27, 1373-1380, 1996). Resulting NO together with O<sub>2</sub> from infiltrating neutrophils is thought to be responsible for cellular and organ damage. Also, in models of traumatic brain injury (Mesenge et al. J. Neurotrauma 13, 209-214, 1998; Wada et al. Neurosurgery 43, 1427-1436, 1998) NO-synthase inhibitors have been shown to possess protective properties. A regulatory role for inducible NO-synthase has been reported in various tumor cell lines (Tozer & Everett Clin Oncol. 9, 357-264, 1997).

On account of their inducible NO-synthase-inhibiting properties, the compounds according to the invention can be employed in human and veterinary medicine and therapeutics, where an excess of NO or O<sub>2</sub> due to increases in the activity of inducible NO-synthase is involved. They can be used without limitation for the treatment and prophylaxis of the following diseases:

**Acute inflammatory diseases:** Septic shock, sepsis, SIRS, hemorrhagic shock, shock states induced by cytokine therapy (IL-2, TNF), organ transplantation and transplant rejection, head trauma, acute lung injury, ARDS, inflammatory skin conditions such as sunburn, inflammatory eye conditions such as uveitis, glaucoma and conjunctivitis.

**Chronic inflammatory diseases of peripheral organs and the CNS:** gastrointestinal inflammatory diseases such as Crohn's disease, inflammatory bowel disease, ulcerative colitis, lung inflammatory diseases such as asthma and COPD, arthritic disorders such as rheumatoid arthritis, osteoarthritis and gouty arthritis, heart disorders such as cardiomyopathy and myocarditis, arterosclerosis, neurogenic inflammation, skin diseases such as psoriasis, dermatitis and eczema, diabetes, glomerulonephritis; dementias such as dementias of the Alzheimer's type, vascular dementia, dementia due to a general medical condition, such as AIDS-, Parkinson's disease, Huntington's induced dementias, ALS, multiple sclerosis; necrotizing vasculitides such as polyarteritis nodosa, serum sickness, Wegener's granulomatosis, Kawasaki's syndrome; headaches such as migraine, chronic tension headaches, cluster and vascular headaches, post-traumatic stress disorders; pain disorders such as neuropathic pain; myocardial and cerebral ischemia/reperfusion injury.

The compounds may also be useful in the treatment of cancers that express nitric oxide synthase.

The invention further relates to a method for the treatment of mammals, including humans, which are suffering from one of the abovementioned illnesses. The method is characterized in that a therapeutically active and pharmacologically effective and tolerable amount of one or more of the compounds according to the invention is administered to the ill mammal.

The invention further relates to the compounds according to the invention for use in the treatment and/or prophylaxis of illnesses, especially the illnesses mentioned.

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The invention also relates to the use of the compounds according to the invention for the production of pharmaceutical compositions which are employed for the treatment and/or prophylaxis of the illnesses mentioned.

The invention also relates to the use of the compounds according to the invention for the production of pharmaceutical compositions having an iNOS inhibitory activity.

The invention furthermore relates to pharmaceutical compositions for the treatment and/or prophylaxis of the illnesses mentioned, which contain one or more of the compounds according to the invention.

The pharmaceutical compositions are prepared by processes which are known per se and familiar to the person skilled in the art. As pharmaceutical compositions, the compounds according to the invention (= active compounds) are either employed as such, or preferably in combination with suitable pharmaceutical auxiliaries and/or excipients, e.g. in the form of tablets, coated tablets, capsules, caplets, suppositories, patches (e.g. as TTS), emulsions, suspensions, gels or solutions, the active compound content advantageously being between 0.1 and 95% and where, by the appropriate choice of the auxiliaries and/or excipients, a pharmaceutical administration form (e.g. a delayed release form or an enteric form) exactly suited to the active compound and/or to the desired onset of action can be achieved.

The person skilled in the art is familiar with auxiliaries or excipients which are suitable for the desired pharmaceutical formulations on account of his/her expert knowledge. In addition to solvents, gel formers, ointment bases and other active compound excipients, for example antioxidants, dispersants, emulsifiers, preservatives, solubilizers, colorants, complexing agents or permeation promoters, can be used.

The administration of the pharmaceutical compositions according to the invention may be performed in any of the generally accepted modes of administration available in the art. Illustrative examples of suitable modes of administration include intravenous, oral, nasal, parenteral, topical, transdermal and rectal delivery. Oral and intravenous delivery are preferred.

For the treatment of disorders of the respiratory tract, the compounds according to the invention are preferably also administered by inhalation in the form of an aerosol; the aerosol particles of solid, liquid or mixed composition preferably having a diameter of 0.5 to 10 µm, advantageously of 2 to 6 µm.

Aerosol generation can be carried out, for example, by pressure-driven jet atomizers or ultrasonic atomizers, but advantageously by propellant-driven metered aerosols or propellant-free administration of micronized active compounds from inhalation capsules.

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Depending on the inhaler system used, in addition to the active compounds the administration forms additionally contain the required excipients, such as, for example, propellants (e.g. Frigen in the case of metered aerosols), surface-active substances, emulsifiers, stabilizers, preservatives, flavorings, fillers (e.g. lactose in the case of powder inhalers) or, if appropriate, further active compounds.

For the purposes of inhalation, a large number of apparatuses are available with which aerosols of optimum particle size can be generated and administered, using an inhalation technique which is as right as possible for the patient. In addition to the use of adaptors (spacers, expanders) and pear-shaped containers (e.g. Nebulator®, Volumatic®), and automatic devices emitting a puffer spray (Autohaler®), for metered aerosols, in particular in the case of powder inhalers, a number of technical solutions are available (e.g. Diskhaler®, Rotadisk®, Turbohaler® or the inhaler described in European Patent Application EP 0 505 321), using which an optimal administration of active compound can be achieved.

For the treatment of dermatoses, the compounds according to the invention are in particular administered in the form of those pharmaceutical compositions which are suitable for topical application. For the production of the pharmaceutical compositions, the compounds according to the invention (= active compounds) are preferably mixed with suitable pharmaceutical auxiliaries and further processed to give suitable pharmaceutical formulations. Suitable pharmaceutical formulations are, for example, powders, emulsions, suspensions, sprays, oils, ointments, fatty ointments, creams, pastes, gels or solutions.

The pharmaceutical compositions according to the invention are prepared by processes known per se. The dosage of the active compounds is carried out in the order of magnitude customary for iNOS inhibitors. Topical application forms (such as ointments) for the treatment of dermatoses thus contain the active compounds in a concentration of, for example, 0.1-99%. The dose for administration by inhalation is customary between 0.1 and 10 mg per day. The customary dose in the case of systemic therapy (p.o.) is between 0.3 and 30 mg/kg per day, (i. v.) is between 0.3 and 30 mg/kg/h.

**1226EPORD01 2003-09 05****- 27 -****Biological investigations****Measurement of inducible NO-synthase activity**

The assay is performed in 96-well microtiter F-plates (Greiner, Frickenhausen, FRG) in a total volume of 100 µl in the presence of 100 nM calmodulin, 226 µM CaCl<sub>2</sub>, 477 µM MgCl<sub>2</sub>, 5 µM flavin-adenine-dinucleotide (FAD), 5 µM flavin mononucleotide (FMN), 0.1 mM NADPH, 7 mM glutathione, 10 µM BH4 and 100 mM HEPES pH 7.2. Arginine concentrations are 0.1 µM for enzyme inhibition experiments. 150000 dpm of [<sup>3</sup>H]arginine are added to the assay mixture. Enzyme reaction is started by the addition of 4 µg of a crude cytosolic fraction containing human inducible NO-synthase and the reaction mixture is incubated for 45 to 60 min at 37°C. Enzyme reaction is stopped by adding 10 µl of 2M MES-buffer pH 5.0. 50 µl of the incubation mixture are transferred into a MADP N65 filtration microtiter plate (Millipore, Eschborn, FRG) containing already 50 µl of AG-50W-X8 cation exchange resin (Biorad, München, FRG). The resin in the Na<sup>+</sup> loaded form is pre-equilibrated in water and 70 µl (corresponding to 50 µl dry beads) are pipetted under heavy stirring with a 8 channel pipette into the filtration plate. After pipetting 50 µl of the enzyme reaction mixture onto the filtration plates, the plates are placed on a filtration manifold (Porvair, Shepperton, UK) and the flow through is collected in Pico scintillation plates (Packard, Meriden, CT). The resin in the filtration plates is washed with 75 µl of water (1x50 µl and 1x25 µl) which is also collected in the same plate as the sample. The total flow through of 125 µl is mixed with 175 µl of Microscint-40 scintillation cocktail (Packard) and the scintillation plate is sealed with TopSeal P-foil (Packard). Scintillation plates are counted in a scintillation counter.

For the measurement of inducible NO-synthase-inhibiting potencies of compounds increasing concentrations of inhibitors were included into the incubation mixture. IC<sub>50</sub>-values were calculated from the percent inhibition at given concentrations by nonlinear least square fitting.

The inhibitory values determined for the compounds according to the invention follow from the following table A, in which the compound numbers correspond to the example numbers.

**1226EPORD01 2003-09-05****- 28 -****Table A****Inhibition of iNOS activity [measured as -logIC<sub>50</sub> (mol/l)]**

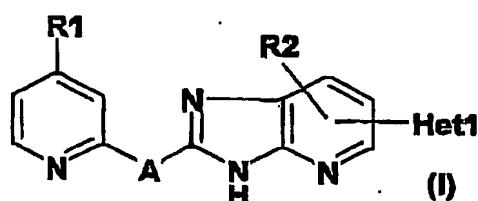
compound	-logIC <sub>50</sub>
1	7.31
2	7.34
3	7.26
4	7.61
5	7.46
6	7.31

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Patent claims

## 1. Compounds of formula I



In which

- R1 is 1-4C-alkoxy,
- A is 1-4C-alkylene,
- R2 is hydrogen, halogen, 1-4C-alkyl or 1-4C-alkoxy,
- Het1 is optionally substituted by R3 and/or R4 and is a monocyclic or fused bicyclic 5- to 10-membered unsaturated or partially saturated heteroaryl radical comprising one to three heteroatoms, each of which is selected from a group consisting of nitrogen, oxygen and sulfur, in which
  - R3 is 1-4C-alkyl, halogen, cyano, trifluoromethyl, phenyl, mono- or di-1-4C-alkylamino, formyl, 1-4C-alkylcarbonyl, carboxyl or 1-4C-alkoxy,
  - R4 is 1-4C-alkyl or halogen,

as well as the salts, N-oxides and the salts of the N-oxides of these compounds.

## 2. Compounds of formula I according to claim 1

in which

- R1 is methoxy,
- A is ethylene,
- R2 is hydrogen,
- Het1 is optionally substituted by R3 and/or R4 and is a monocyclic or fused bicyclic 5- to 10-membered unsaturated or partially saturated heteroaryl radical comprising one to three heteroatoms, each of which is selected from a group consisting of nitrogen, oxygen and sulfur, in which
  - R3 is 1-4C-alkyl, halogen, cyano, trifluoromethyl, phenyl, mono- or di-1-4C-alkylamino, formyl, 1-4C-alkylcarbonyl, carboxyl or 1-4C-alkoxy,
  - R4 is 1-4C-alkyl or halogen,

as well as the salts, N-oxides and the salts of the N-oxides of these compounds.

## 3. Compounds of claim 1 or claim 2 under the proviso that 2-[2-(4-methoxypyridin-2-yl)ethyl]-6-(pyridin-3-yl)-3H-imidazo[4,5-b]pyridine is thereof disclaimed,

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as well as the salts, N-oxides and the salts of the N-oxides of these compounds.

**4. Compounds of claim 1 or claim 2**

under the proviso that hereby

Het1 is not pyridyl, and

Het1 is not pyridyl substituted by R5 wherein

R5 is halogen, 1-4C-alkyl or 1-4C-alkoxy,

as well as the salts, N-oxides and the salts of the N-oxides of these compounds.

**5. Compounds of formula I according to any of the preceding claims, in which**

Het1 is optionally substituted by R3 and/or R4 and is a monocyclic 5-membered unsaturated heteroaryl radical comprising one to three heteroatoms, each of which is selected from a group consisting of nitrogen, oxygen and sulfur,

or

Het1 is optionally substituted by R3 and/or R4 and is a monocyclic 6-membered unsaturated heteroaryl radical comprising two nitrogen atoms,

or

Het1 is optionally substituted by R3 and/or R4 and is a fused bicyclic 9- or 10-membered unsaturated or partially saturated heteroaryl radical comprising one to three heteroatoms, each of which is selected from a group consisting of nitrogen, oxygen and sulfur,

in which

R3 is 1-4C-alkyl, halogen, cyano, trifluoromethyl, phenyl, mono- or di-1-4C-alkylamino, formyl, 1-4C-alkylcarbonyl, carboxyl or 1-4C-alkoxy, and

R4 is 1-4C-alkyl or halogen;

or

Het is R3- and R4-substituted pyridyl,

in which

R3 is 1-4C-alkyl or halogen, and

R4 is 1-4C-alkyl or halogen;

as well as the salts, N-oxides and the salts of the N-oxides of these compounds.

**6. Compounds of formula I according to claim 1, in which**

R1 is methoxy,

A is ethylene,

R2 is hydrogen,

Het1 is optionally substituted by R3 and/or R4 and is a thiophenyl radical, in which

R3 is 1-4C-alkyl, chlorine, cyano, phenyl, dimethylamino, formyl, acetyl or carboxyl, and

R4 is 1-4C-alkyl,

or

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Het1 is optionally substituted by R3 and is a furanyl radical, in which  
 R3 is 1-4C-alkyl,  
 or  
 Het1 is optionally substituted by R3 and/or R4 and is a pyridyl radical, in which  
 R3 is 1-4C-alkyl, chlorine, fluorine, 1-4C-alkoxy or carboxyl, and  
 R4 is 1-4C-alkyl or chlorine,  
 or  
 Het1 is an indolyl, benzothiophenyl, benzofuranyl, benzoxaloyl, benzothiazolyl, quinolyl or isoquinolyl radical,  
 under the proviso that 2-[2-(4-methoxypyridin-2-yl)ethyl]-6-(pyridin-3-yl)-3H-imidazo-[4,5-b]pyridine is thereof disclaimed,  
 as well as the salts, N-oxides and the salts of the N-oxides of these compounds

## 7. Compounds of formula I according to claim 1, in which

R1 is methoxy,  
 A is ethylene,  
 R2 is hydrogen,  
 Het1 is optionally substituted by R3 and/or R4 and is a thiophenyl radical, in which  
 R3 is 1-4C-alkyl, chlorine, cyano or phenyl, and  
 R4 is 1-4C-alkyl,  
 or  
 Het1 is optionally substituted by R3 and is a furanyl radical, in which  
 R3 is 1-4C-alkyl,  
 or  
 Het1 is a R3- and R4-substituted pyridyl radical, in which  
 R3 is 1-4C-alkyl, chlorine or fluorine, and  
 R4 is chlorine,  
 or  
 Het1 is an indolyl, benzothiophenyl, benzofuranyl, benzoxaloyl, benzothiazolyl, quinolyl or isoquinolyl radical,  
 as well as the salts, N-oxides and the salts of the N-oxides of these compounds.

## 8. Compounds of formula I according to claim 1, in which

R1 is methoxy,  
 A is ethylene,  
 R2 is hydrogen,  
 Het1 is optionally substituted by R3 and/or R4 and is a thiophenyl radical, in which  
 R3 is methyl, chlorine, cyano or phenyl, and  
 R4 is methyl,

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or

Het1 is optionally substituted by R3 and is a furanyl radical, in which

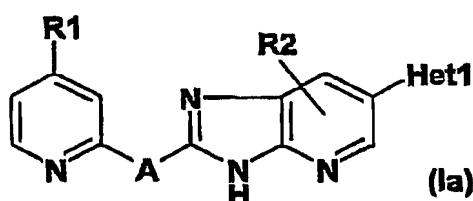
R3 is methyl,

or

Het1 is an indolyl radical,

as well as the salts, N-oxides and the salts of the N-oxides of these compounds.

## 9. Compounds of claim 1, wherein said compounds have the formula Ia



in which

R1 is methoxy,

A is ethylene,

R2 is hydrogen,

Het1 is pyridin-4-yl, pyridin-2-yl, 3-fluoro-pyridin-4-yl, 3-chloro-pyridin-4-yl, 6-fluoro-pyridin-3-yl, 6-chloro-pyridin-3-yl, 2-fluoro-pyridin-3-yl, 2-chloro-pyridin-3-yl, 4-methyl-pyridin-2-yl, 5-methyl-pyridin-2-yl, 6-methyl-pyridin-2-yl, 5-methyl-pyridin-3-yl, 2-methyl-pyridin-4-yl, 3-methyl-pyridin-4-yl, 6-methoxy-pyridin-2-yl, 2-methoxy-pyridin-3-yl, 4-methoxy-pyridin-3-yl, 5-methoxy-pyridin-3-yl or 6-methoxy-pyridin-3-yl,

as well as the salts, N-oxides and the salts of the N-oxides of these compounds.

## 10. Compounds of formula I according to any of the preceding claims for the treatment of diseases.

## 11. Pharmaceutical compositions containing one or more compounds of formula I according to any of the preceding claims together with the usual pharmaceutical auxiliaries and/or excipients.

## 12. Use of compounds of formula I according to any of the preceding claims for the production of pharmaceutical compositions for the treatment of acute inflammatory diseases.

## 13. Use of compounds of formula I according to any of the preceding claims for the production of pharmaceutical compositions for the treatment of chronic inflammatory diseases of peripheral organs and the CNS.

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- 14.** A method for treating acute inflammatory diseases in a patient comprising administering to said patient a therapeutically effective amount of a compound of formula I according to any of the preceding claims.
  
- 15.** A method for treating chronic inflammatory diseases of peripheral organs and the CNS in a patient comprising administering to said patient a therapeutically effective amount of a compound of formula I according to any of the preceding claims

**1226EPORD01 2003-09 05****- 34 -****Abstract**

The compounds of formula I in which R1, R2, Het1 and A have the meanings as given in the description are novel effective iNOS inhibitors.

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